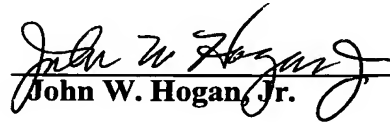


Applicants believe that the present application is in condition for allowance and respectfully request that the Examiner enter the amendment and allow the application. Favorable treatment of the application is earnestly solicited.

  
John W. Hogan, Jr.

Reg. No. 32,703

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**Version with Markings to Show Changes Made**

**In the Specification**

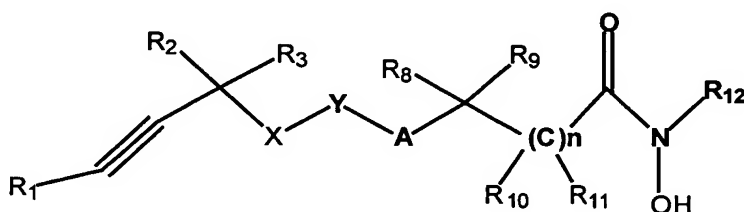
Please replace the paragraph beginning on page 1, line 4, with the following:

This is a divisional of copending application serial no. 09/492,686 filed on January 27, 2000, which application claims the benefit of U.S. Provisional Application No. 60/155,184 filed January 27, 1999, the entire disclosure of each being hereby incorporated by reference.

~~This application claims the benefit of U.S. Provisional Application No. 60/155,184, filed January 27, 1999.~~

**In the Claims**

1. A compound of formula



wherein:

R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl;

R<sub>2</sub> and R<sub>3</sub> are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R<sub>7</sub> is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R<sub>1</sub>, -SO<sub>2</sub>-R<sub>1</sub>, -C(O)-NHR<sub>1</sub>, -C(O)NR<sub>5</sub>R<sub>6</sub>, -C(O)R<sub>1</sub>NR<sub>5</sub>R<sub>6</sub>, -C(O)-OR<sub>1</sub>, -C(NH)-NH<sub>2</sub>.

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R<sub>8</sub> and R<sub>9</sub>, R<sub>9</sub> and R<sub>10</sub> or R<sub>10</sub> and R<sub>11</sub>, together with the carbon atom or atoms to

which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl ring;

R<sub>12</sub> is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

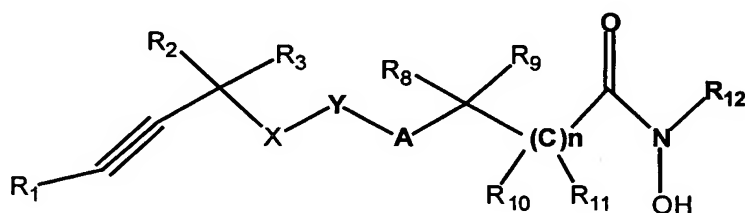
A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R<sub>8</sub> and R<sub>9</sub> together with the carbon atom to which they are attached may not form a piperdinyl or tetrahydropyranyl ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

4. A method of inhibiting pathological changes mediated by TNF- $\alpha$  converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula



I

wherein:

R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl;

R<sub>2</sub> and R<sub>3</sub> are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH<sub>3</sub>;

R<sub>7</sub> is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R<sub>1</sub>, -SO<sub>2</sub>-R<sub>1</sub>, -C(O)-NHR<sub>1</sub>, -C(O)NR<sub>5</sub>R<sub>6</sub>, -C(O)R<sub>1</sub>NR<sub>5</sub>R<sub>6</sub>, -C(O)-OR<sub>1</sub>, -C(NH)-NH<sub>2</sub>.

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R<sub>8</sub> and R<sub>9</sub>, R<sub>9</sub> and R<sub>10</sub> or R<sub>10</sub> and R<sub>11</sub>, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl ring;

R<sub>12</sub> is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

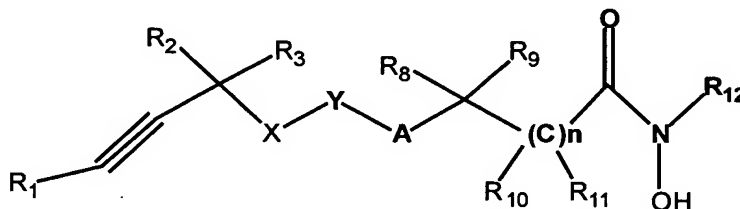
A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R<sub>8</sub> and R<sub>9</sub> together with the carbon atom to which they are attached may not form a piperdinyll or tetrahydropyranyll ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound having the formula



I

wherein:

R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl;

R<sub>2</sub> and R<sub>3</sub> are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH<sub>3</sub>;

R<sub>7</sub> is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)-R<sub>1</sub>, -SO<sub>2</sub>-R<sub>1</sub>, -C(O)-NHR<sub>1</sub>, -C(O)NR<sub>5</sub>R<sub>6</sub>, -C(O)R<sub>1</sub>NR<sub>5</sub>R<sub>6</sub>, -C(O)-OR<sub>1</sub>, -C(NH)-NH<sub>2</sub>.

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R<sub>8</sub> and R<sub>9</sub>, R<sub>9</sub> and R<sub>10</sub> or R<sub>10</sub> and R<sub>11</sub>, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl ring;

R<sub>12</sub> is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and with the further proviso that if Y is phenyl, then R<sub>8</sub> and R<sub>9</sub> together with the carbon atom to which they are attached may not form a piperdinyll or tetrahydropyranyll ring; and

n is 0-2; or a pharmaceutically acceptable salt thereof.